Diagnosis and Therapy of Drug and Chemical Toxicity

(NIH Award # P20RR20654)

Brij Moudgil, Tim Morey, Steve Roberts

Interdisciplinary Research Centers Workshop

NIH Campus; Bethesda, MD

February 9, 2006

UNIVERSITY OF FLORIDA

PERC Particle Engineering Research Center

National Science Foundation Engineering Research Center for Particle Research and Technology at the University of Florida

Background & Significance

- More than 4 million poisoning episodes occur each year in the US[1]
- In 2001, poisoning was the second leading injury related cause of fatality[1]
- Drug and Chemical poisonings cost the US ~$13 billion per year[2]

Clinical management of drug & chemical toxicity is severely handicapped

- **Diagnosis**
- **Reversal**

[1] Institute of Medicine. Forging a Poison Prevention and Control System. The National Academies Press. Washington, DC. 2004.

[2] Ibid

Objectives

Develop, promote, and implement an interdisciplinary approach for improving the diagnosis and treatment of drug and chemical toxicity.

Specific Aims

1) Create a planning structure through which individuals from a variety of relevant disciplines can interact, research strategies can be developed, and institutional barriers to collaborative research can be addressed.

2) Identify and minimize institutional barriers to interdisciplinary collaboration.

Specific Aims (contd.)

3) **Identify specific problems in the diagnosis and treatment of toxicity and develop research strategies to solve them.**

4) **Conduct pilot research to test the feasibility of selected research strategies identified in Aim 3 and to validate the planning approach.**

Team Members

Name	*Expertise*	*Name*	*Expertise*
D. Shah	Biophysics / Chem. Eng	C. Martin	Nano-bio Interface
R. Dickenson	Biophysics / Chem. Eng.	P. Holloway	Nanostructured Materials
B. Koopman	Environ. Eng.	W. Tan	Aptamer Chemistry, NP Synth.
K. Powers	Particle Sci./Technol.	G. Erdos	Biotechnol. / Electron Micro.
H. El-Shall	Bioparticle Synth./ Materials	M. Popp	Biotechnology/ Microbiology
B. Moudgil	Interfacial Phenomena	J. LePine	Behavioral Psychology
T. Morey	Anesthesiology/ Nano.	E. Young	Communication
W. Sigmund	Nanoparticle Synthesis	A. Brennan	Biopolymers
E. Sander	Management/ Intel. Prop.	C. Batich	Biomaterials
A. Donnelly	Interdisciplinary Education	E. Scott	Stem Cells, Molec. Genetics
D. Dennis	Anesthesiology/ Pharm.	G. Walters	Physiology, Bioimaging
J. Long	Protein Chemistry	H. Jiang	Bioimaging
D. Purich	Enzymology	R. Mercle**	Neurosurgery
K. Berns	Gene Therapy	V. Antony	Pulmonary Medicine
S. Santra*	Chemistry/ Particle Synthesis	A. Chauhan	BioChemE
E. Sobel	Immunology	M. Varshney	Surface Chem
S. Roberts	Environ./ Human Toxicology		

** University of Central Florida*
*** Vanderbilt University*

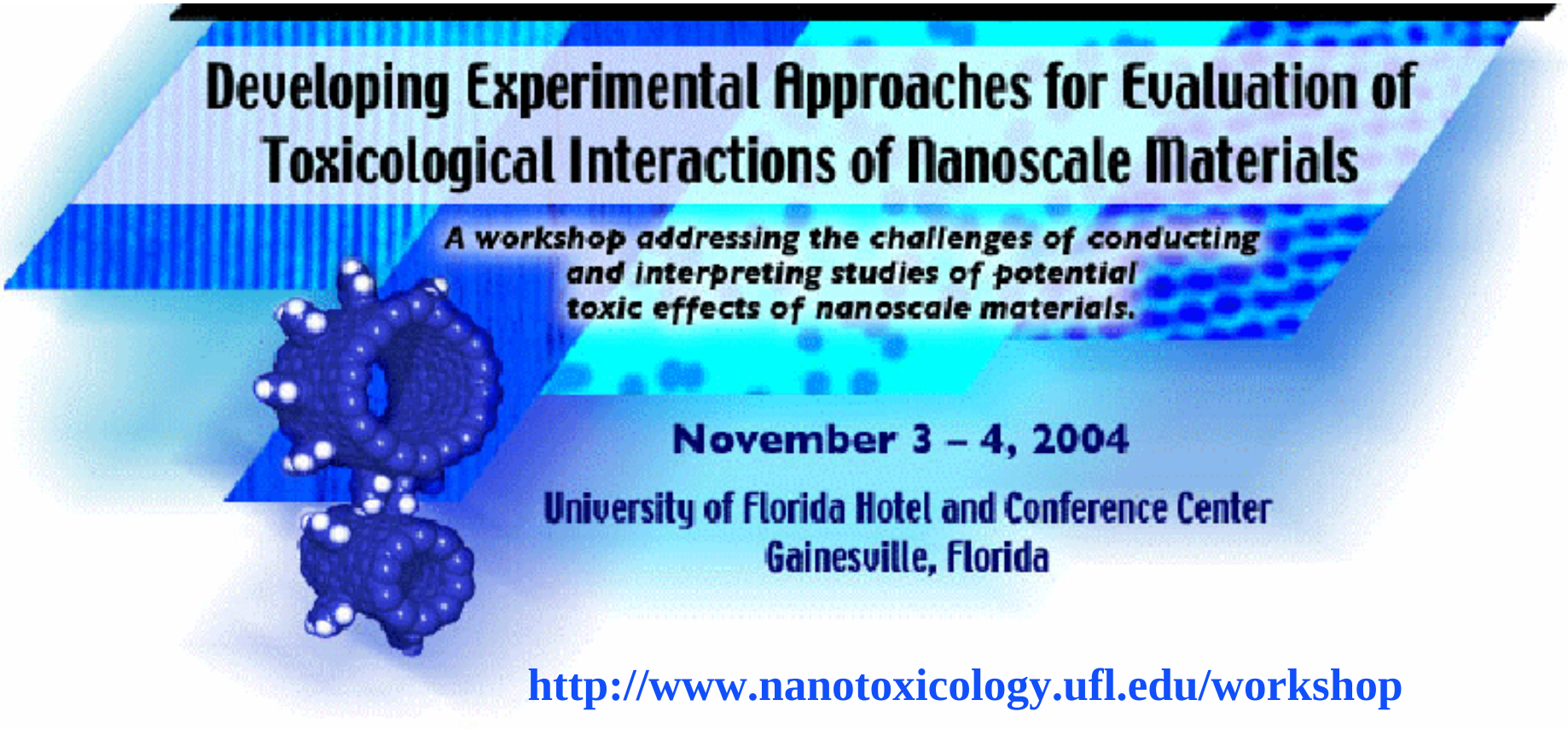
Team Development

- **Most team members aware of each other's research at least on bilateral basis**
- **New team members recruited to meet interdisciplinary expertise needs**
- **Development tools for common understanding**
  - Meetings, informal tutorials (e.g., cell biology, engineered systems approach)
  - Placing students/post docs in each others labs most helpful
  - Offices in each others departments not successful

Meetings/Events

- Biweekly team meetings, smaller ad-hoc meetings
- Nanotoxicology Workshop, Nov. 3-4, 2004
- Drs. Farber and Balshaw's visit, Feb. 24, 2005
- Interdisciplinary Education & Training Workshop, May 2-3, 2005
- International Symposium, Role of Adsorbed Films and Particulate Systems in Nano and Bio-technologies, August, 24-26, 2005
- Visits to Companies and other Centers, Nov, 2004 -

Nanotoxicology Workshop



http://www.nanotoxicology.ufl.edu/workshop

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Interdisciplinary Education & Training Workshop at UF, May 2-3, 2005

- **Institutional Barriers identified**
- **New disciplines vs. combined disciplines**
- **Towards a unified strategy for ID education at UF**
  - Synergism with current programs
- **Identification of foundation coursework**
- **Cross-training strategies for biologist and physical scientists**
- **Building of an Interdisciplinary Student Culture**
- **Student & Faculty Perspectives**

Management Team Structure

University Advisory Panel

Win Phillips	***(UF VP for Research)***
P. Khargonekar	***(Dean COE)***
N. Sullivan	***(Dean CLAS)***
C. Tisher	***(Dean COM)***

Leadership Core

Dennis, Donnelly, Martin, Morey, Moudgil, Roberts & Sanders

Policy Planning Team

Leadership Core

Management Expert	**Sanders**
Organizational Behavior Expert	**LePine**
3 ad hoc Rotating Members	

Technical Planning Team

All Researchers

Rapid Response Teams

Donnelly& Long	**Cross-training Strategies**
Dennis, Moudgil & Sanders	**Comm. Upper Admin.**
Morey & Roberts	**Nanotoxicity Issues**

Group Evaluation

- **Dr. Jeff LePine, Business School - expertise in interdisciplinary team development evaluated and suggested optimal techniques for team building and functioning**
- **Participated in team meetings and provided informal input to the entire team**
- **Provided useful input to the center director for improving the productivity of discussions**
  - Structured vs. free flowing discussions
  - Equal opportunity for all team members to express their views

Research Coordination

- Each PI to have control of project funds and responsibility for timely completion of tasks
- PIs to align research scope with other projects in consultation with Technical Planning Team
- Policy Planning Team responsible for overall coordination
- Center PI -Overall responsibility including communication of Progress and Mid-Course Corrections to NIH

Institutional Support

- **VP-Research, Deans supportive of interdisciplinary research**
- **Adequate career path for team members exist at UF**
- **Interdisciplinary contributions favorably considered in T & P decisions**
- **Team positively impacted by access to upper administration**
  - Opportunity fund for interdisciplinary seed projects
  - Streamlining of proposal approval and cost sharing decisions

Potential Research Areas

DETECTION

Novel approaches to the selective binding of drug and chemical toxicants **Scientific Foundation for development of new diagnostic and treatment technologies.**

Integration into Devices Development of new sensors for exposure and for biological effects that are precursors to toxicity could improve the ability to diagnose, treat, and prevent toxicity

REVERSAL

Blanket inactivation of toxicants **ME/NP systems for reversal of multiple potential toxicants**

Targeted inactivation of toxicants **How to create catalytic sites on nanostructures to degrade toxicant molecules with some degree of specificity**

PREVENTION

Targeted protection against toxicity Nanodevices to deliver stress protein genes to selected tissue targets

Toxicity of nanodevices and nanostructures Nanostructures and nanodevices offer the possibility of innovative new solutions to medical problems, but the health consequences of their use are largely unknown

Engineered Systems Approach to Addressing Biomedical Challenges

- A Pilot Research Project -

Particle Engineering Research Center

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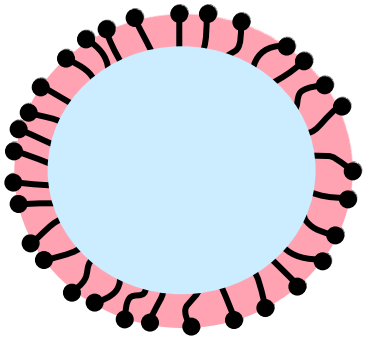
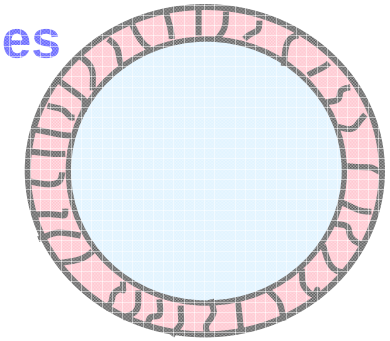
Particulate Systems for Drug Detoxification



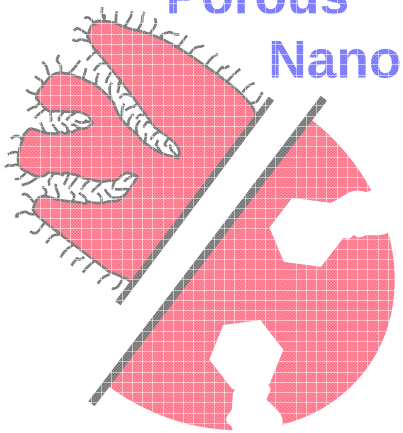
Micro-
emulsion

D. Shah, Chem Eng.
T. Morey, Anesth.
D. Dennis, Anesth.
M. Varshney, Anesth.
A. Chauhan, Chem Eng.

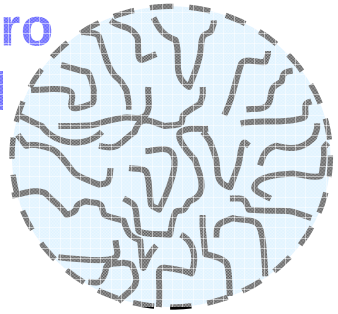
Micro/Macro Emulsion
Mediated Core-Shell
Nanoparticles



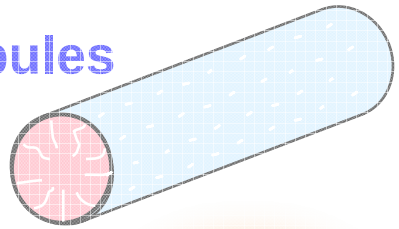
Sol-gel Mediated
Porous
Nanoparticles



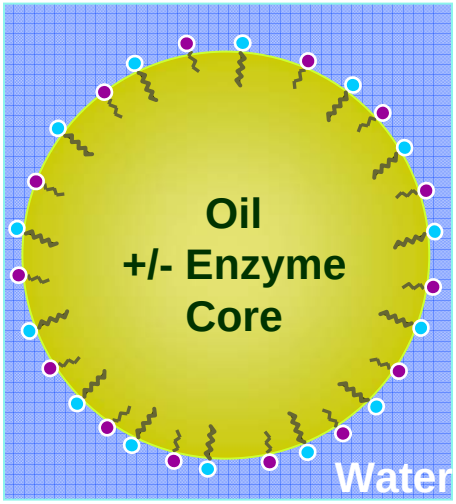
Micro
-gel

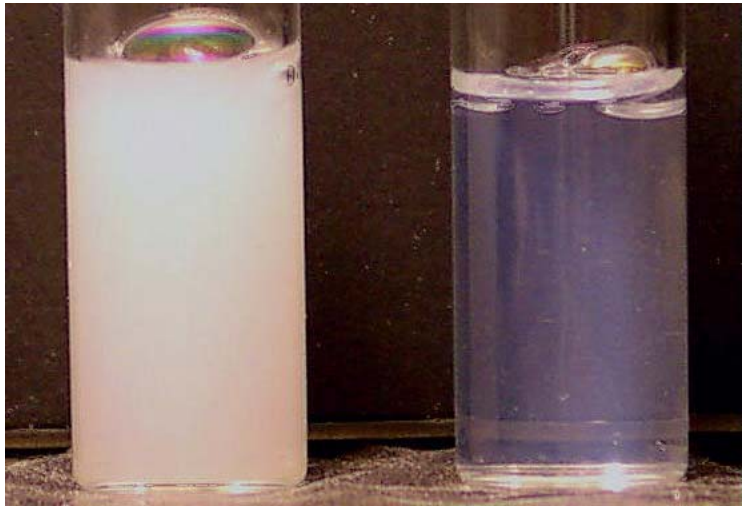


Nanotubules



Microemulsions for Drug Detoxification



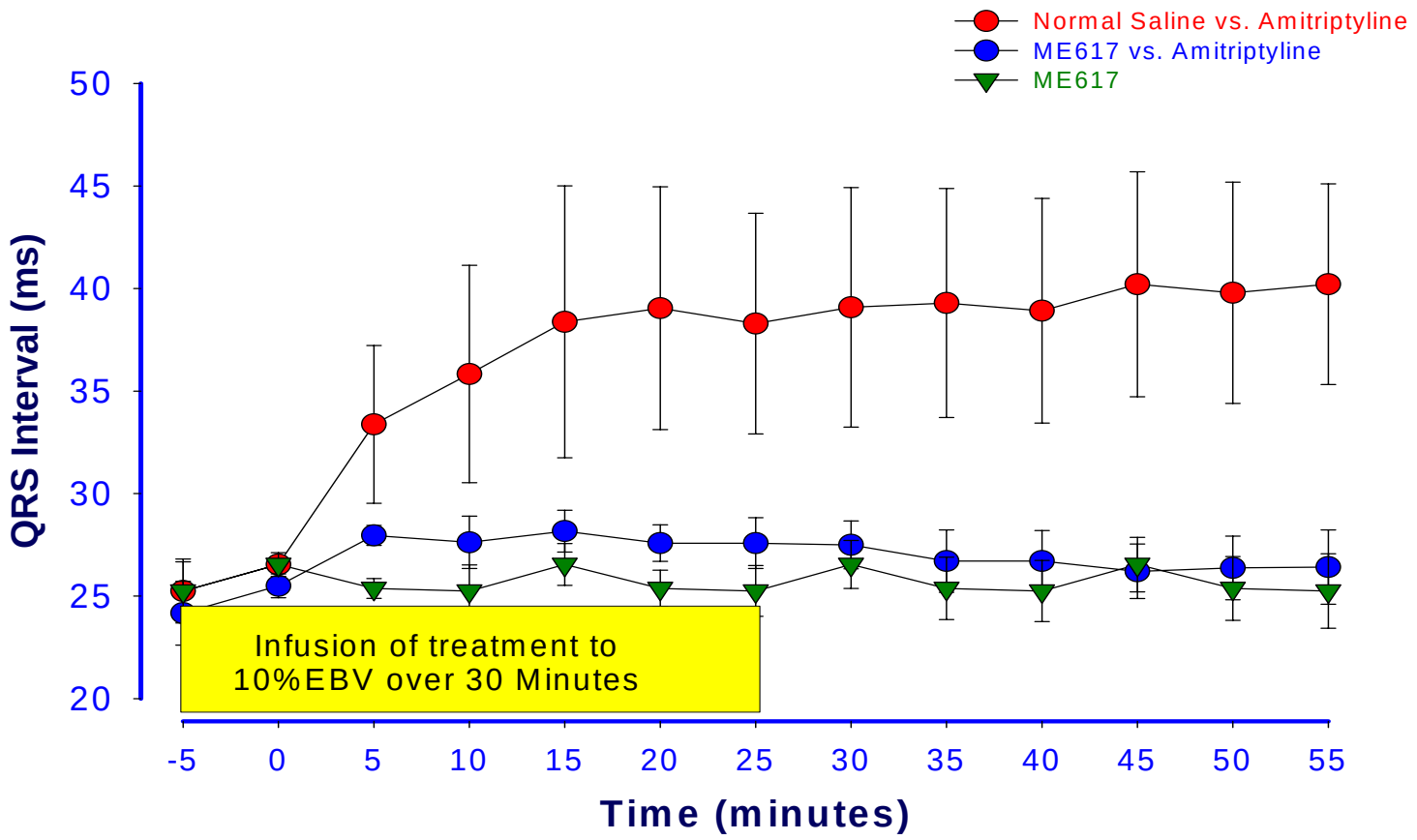


	Emulsion	Microemulsion
Particle Size :	**~ 400 nm**	**~ 30 nm**
Surface Area :	**~ 15 m^2/ml**	**~ 215 m^2/ml**

- **Thermodynamically stable nanoparticulates**
- **Engineered surfactant/co-surfactant shell and lyophillic core**

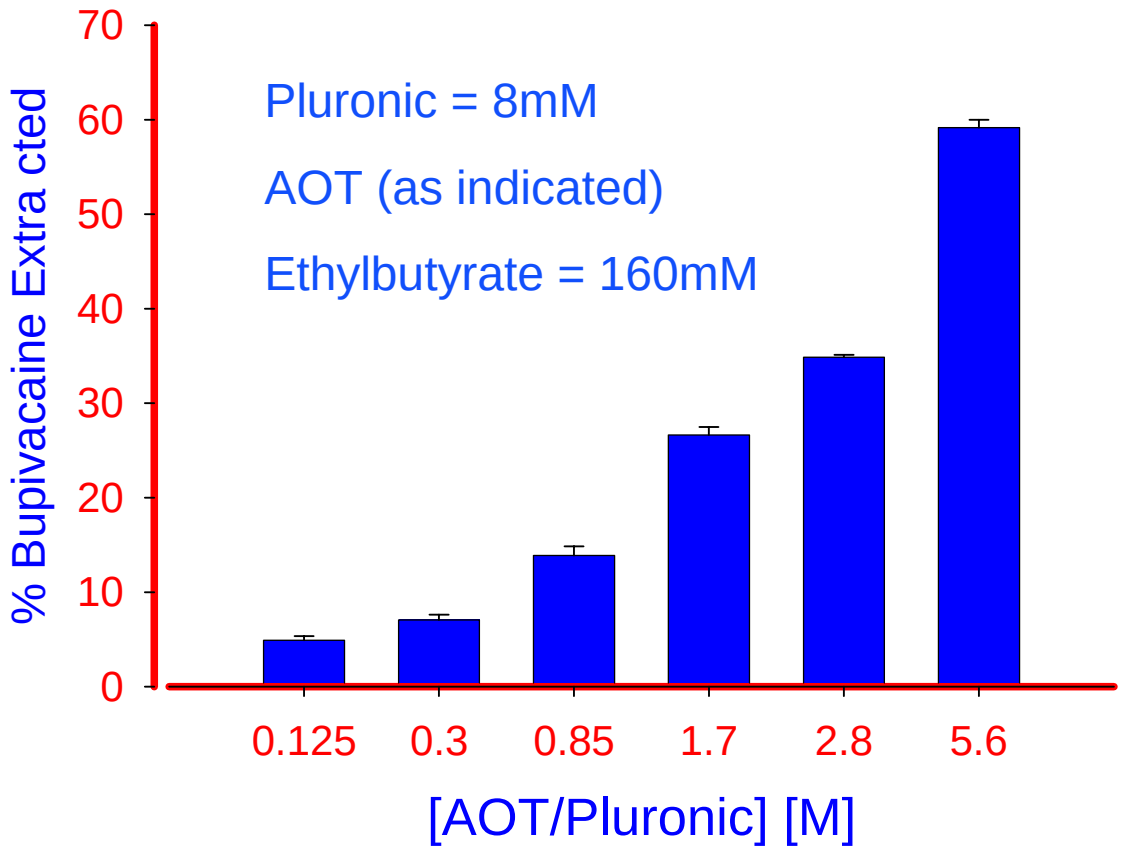
Courtesy of Morey, T., Partch, D., Shah, D. and Varshney, M.

Effect of ME617 (0.05%$_{v/v}$ oil, blood) on Amitriptyline toxicity in living rat



ME617 effective for Amitriptyline toxicity reversal but not for Bupivicane

ME Reformulated for Bupivicane Extraction



Concluding Remarks

- **Management Team Structure Implemented**
- **Institutional Barriers to ID Research Identified and Communicated to Upper Administration**
- **Cross-Training Strategies Identified**
- **Engineered Systems Approach successfully applied to ME detoxification research**
- **Interdisciplinary Research much like Jazz Ensemble**

Interdisciplinary Team → **Jazz Ensemble**